All in Good Fun

A brief walk through the history of science uncovers many famous collaborators whose discoveries have changed the world. Pierre and Marie Curie, James Watson and Francis Crick, Michael Bishop and Harold Varmus, to name just a few. Some came together for one brief shining discovery; others had a lifetime commitment to a shared research agenda. Asking what makes for a successful collaboration may be like asking what makes for any successful relationship, and may be as difficult to answer. Michael Gottesman, M.D., and Ira Pastan, M.D., came together at the NCI in the 1970s to uncover the molecular basis for the multidrug resistance (MDR) that develops in cellular diseases ranging from cancer to bacterial infections. Whether it is because "opposites attract" or because of "shared mutual interests," according to Gottesman and Pastan, the hallmark of a successful collaboration is that it is just plain fun.

"Michael was interested in somatic cell genetics and I was interested in biochemistry," recalled Pastan, who is now Chief of CCR's Laboratory of Molecular Biology. "And, you know, genetics plus biochemistry equals molecular biology."

Pastan was interested in the role of the intracellular signaling molecule cyclic adenosine monophosphate (cAMP) in limiting the growth of cancer cells. Gottesman, who is now Chief of CCR's Laboratory of Cell Biology, suggested that as a new way into the problem, they make mutant cell lines (from Chinese hamster ovary, or CHO, cells) that did not respond to cAMP and study their properties.

"At that point, Ira had gotten some space and I hired a postdoc and we began to isolate mutants that were resistant to cAMP," explained Gottesman.

At this juncture, so the story goes, Bruce Chabner, M.D., who was the Head of the Cancer Chemotherapy Division of the NIH, pointed out that the phenomenon of multidrug resistance was a major reason that chemotherapy fails in patients. Chemotherapy itself was a relatively new innovation pioneered by the NIH and was universally hailed as being highly successful until people became resistant to the treatments. Chabner, therefore, asked: "Why don't you actually study resistance in a model relevant to human cancer?"

"Resources were limited," remembered Gottesman, "but the clinical relevance of drug resistance was clear at a time when Ira was moving away from very basic biology to much more focused applications to cancer. This seemed like a good transition. So we started to study how cancer cells become resistant to chemotherapy."

Different Styles Can Be Complementary

Gottesman and Pastan both have medical degrees but had decided early on to move into more basic research. In preparing to tackle resistance to chemotherapy, they decided to participate in clinical rounds once a week and to ask questions. "NIH was the place where chemotherapy was initiated, so this was a great re-education," said Gottesman.

The goal was to develop tools for the clinical evaluation of drug

(*Photo: R. Baer*)

Michael Gottesman, M.D., and Ira Pastan, M.D.

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resistance, which meant using human cell lines. Furthermore, they wanted the reagents, antibodies, and whatever else they developed to be relevant to the clinic.

"I tried to define in the beginning what our contributions were," said Pastan, "but basically we just liked working together. It was a problem we were both clearly interested in. This was not a shotgun marriage; we found each other and a mutual interest. We enjoyed talking to each other."

"I was in the lab 100 percent of the time in those days and we just had a good time," said Gottesman. "We were exactly on the same wavelength. We came up with a plan, usually quickly. But neither of us is entrenched in our way of doing science."

"We had somewhat different orientations in terms of science but each appreciated the other's discipline," added Pastan. "Although you can't be an expert in every field, you have to be conversant in the language. We just had a lot of fun. We both enjoy a certain kind of humor and both enjoyed interacting with the fellows."

"One of the major principles I learned from Ira is that you shouldn't be technically limited," said Gottesman. "One great advantage of the NIH is that there is always somebody down the hall or across the campus that has the knowledge you need. We depended a lot on people at the NIH."

"We had weekly data meetings," remembered Pastan. "Michael was the good guy, and I was the bad guy. I am very systematic in the practice of science and try to teach people to organize their thoughts accordingly. If I ask 'Why did you do this?', then 'I thought it would be interesting,' is not a good answer. Doing science, you have to be pretty focused. After all, life is short."

"And after the meeting, I'd tell them that Ira was just trying to help and explain what he meant," said Gottesman. "Ira is enormously capable of figuring out the shortest distance; I'm a little more grandiose. Everyone needs two parents."

"I have heard that there are some people who work together who do not have as comfortable a relationship. I think there are different styles," noted Pastan.

Successful Scientists Make Successful Teams

"I think we would have been successful or not in different ways regardless of whether we worked together," said Pastan. "How do you identify a person who will be successful? It is wonderful to be smart and focused, but it isn't sufficient. Some people have the knack of seeing problems and solving them—maybe they have a bit of luck—and some people don't, even though they may be smarter."

Pastan pointed out that usually there is an excess of problems to solve. "Somehow, people who like to do research—they look around and they can sort of figure out something that nobody else is doing that would be of some interest. I have people who come to me and say, 'I can't think of what to do.' Some people have a knack of finding important, novel things to study and if they don't, they should be doing something else."

Pastan concedes that there is luck involved, too. "You can be focused and hard working, but life is full of these chances. You go to a seminar and you hear something and say 'Oh my God, maybe…'"

The fellows that Pastan and Gottesman worked with over the years form an illustrious cadre. "Ira's first postdoc was Harold Varmus!" said Gottesman, referring to the Nobel Laureate and current NCI Director. "And when I interviewed Harold, I turned down Mike Brown!" retorted Pastan, referring to another Nobel Laureate.

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"We had a postdoc application from a well-established scientist in Japan, Shin-Ichi Akiyama, who developed multidrug resistant cell lines that became the basis of most of our studies," said Gottesman. "In fact, the entire pharmaceutical industry uses these cell lines to pretest their drugs."

"If you look at the 50 to 60 postdocs who worked on MDR over the years, virtually all are still working scientists," concluded Pastan.

What, When, and Where Also Matter

"And then there's when to get in a field," said Pastan. "My feeling is that I wouldn't want to work in a field filled with bright people, because it would be kind of boring. What I think is fun is identifying a new area—that's why the MDR project was fun. It was a new area and clearly important, but not much was known.

"And I would expand that to include much of the intramural program—it's always easy to do incremental science and it could be extremely important, but it is much more fun to work in a completely unknown area and make really seminal discoveries."

As he once taught Gottesman long ago, Pastan continues to stress the need to not be limited by technology. "Be broad in your reading of basic biological and clinical literature, and find the people who can help you—for one person to tackle an important problem, it is virtually impossible.

"When I first came to the NIH, I worked in a group studying thyroid hormones," added Pastan. "There were seven people each with a project and they were doing everything I could think of to do. So instead of working on the thyroid gland itself, I decided to work on thyroid stimulating hormone. There was a guy down the hall purifying it, so I had rare access."

(Photo: R. Baer)

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Moving On

Pastan and Gottesman no longer have any joint projects.

"I had to decide whether to work on immunotoxins where I thought we could get drugs into the clinic in my lifetime or MDR where we'd have to rely on companies to develop the drugs," said Pastan. "So one day I said I can't do MDR anymore. It seems like yesterday, but it was 12 years ago."

"I haven't formed the same kind of partnership again," said Gottesman, who has less time to devote to his lab now that he is also Deputy Director for the NIH Office of Intramural Research.

Pastan speaks of a few past collaborations that had some of the same close feeling. For example, he worked closely with Robert Perlman, Ph.D., on cAMP gene regulation in the bacterium *Escherichia coli*. "Bob and I were like two high school kids on the phone late at night, talking about science."

Despite the lack of joint projects, Pastan and Gottesman remain fast friends. "One of the reasons that we so enjoyed the collaboration is that we actually liked each other," said Pastan. "The role that plays in developing long-term collaborations is not a trivial one."

To learn more about Dr. Gottesman's research, please visit his CCR Web site at http://ccr.cancer.gov/staff/staff.asp?Name=mgottesman.

To learn more about Dr. Pastan's research, please visit his CCR Web site at http://ccr.cancer.gov/staff/staff.asp?Name=pastan.